The ClinGen Evidence Repository is an **FDA-recognized human genetic variant database** containing expert-curated assertions regarding variants' pathogenicity and supporting evidence summaries. [Disclaimer]

Variant: NM_000022.4(ADA):c.956_960del (p.Glu319fs)

Version: 1.0

CA274927

193544 (ClinVar)

Gene: ADA (HGNC:100)
Condition: adenosine deaminase deficiency (MONDO:0007064)
Inheritance Mode: Autosomal recessive inheritance
UUID: f5e0c459-540d-4448-82fb-72969aecd4c0
Approved on: Mon, 28 Sep 2026 00:00:00 +0000
Published on: Tue, 27 Oct 2026 00:00:00 +0000

HGVS expressions

NM_000022.4(ADA):c.956_960del (p.Glu319fs)
NM_000022.4:c.956_960del
NC_000020.11:g.44621034_44621038del
CM000682.2:g.44621034_44621038del
NC_000020.10:g.43249675_43249679del
CM000682.1:g.43249675_43249679del
NC_000020.9:g.42683089_42683093del
NG_007385.1:g.35699_35703del
ENST00000492931.6:n.1123_1127del
ENST00000536076.2:c.803_807del
ENST00000536532.6:c.*99_*103del
ENST00000537820.2:c.884_888del
ENST00000539235.6:c.*340_*344del
ENST00000695889.1:c.431_435del
ENST00000695890.1:n.4451_4455del
ENST00000695891.1:c.496_500del
ENST00000695927.1:c.1034_1038del
ENST00000695949.1:c.881_885del
ENST00000695956.1:c.111_115del
ENST00000695957.1:c.*447_*451del
ENST00000695991.1:c.494_498del
ENST00000695992.1:c.*99_*103del
ENST00000695993.1:c.956_960del
ENST00000695994.1:c.*99_*103del
ENST00000695995.1:c.566_570del
ENST00000695996.1:n.1038_1042del
ENST00000696003.1:n.2740_2744del
ENST00000696004.1:n.1124_1128del
ENST00000696005.1:c.406_410del
ENST00000696006.1:c.*99_*103del
ENST00000696007.1:c.883_887del
ENST00000696008.1:n.3310_3314del
ENST00000696017.1:c.953_957del
ENST00000696034.1:c.*99_*103del
ENST00000696035.1:n.1142_1146del
ENST00000696036.1:n.1657_1661del
ENST00000696037.1:n.2633_2637del

ENST00000696038.1:c.*713_*717del
ENST00000696039.1:n.1320_1324del
ENST00000696058.1:c.953_957del
ENST00000696059.1:c.*901_*905del
ENST00000696060.1:c.1025_1029del
ENST00000696061.1:c.953_957del
ENST00000696062.1:c.1019_1023del
ENST00000696063.1:c.1031_1035del
ENST00000696064.1:c.803_807del
ENST00000696065.1:c.278_282del
ENST00000696072.1:n.311_315del
ENST00000696073.1:n.1267_1271del
ENST00000696074.1:n.507_511del
ENST00000696075.1:c.*926_*930del
ENST00000696076.1:c.1025_1029del
ENST00000696077.1:c.950_954del
ENST00000696078.1:c.953_957del
ENST00000696079.1:c.953_957del
ENST00000696080.1:c.956_960del
ENST00000696081.1:n.1075_1079del
ENST00000696082.1:c.1031_1035del
ENST00000696083.1:n.1913_1917del
ENST00000696084.1:n.1133_1137del
ENST00000696104.1:c.*25_*29del
ENST00000372874.9:c.956_960del
ENST00000372874.8:c.956_960del
ENST00000372887.5:c.152-2899_152-2895del
ENST00000464097.5:n.706_710del
ENST00000492931.5:n.1116_1120del
ENST00000536532.5:c.*99_*103del
ENST00000537820.1:c.884_888del
ENST00000539235.5:c.*340_*344del
NM_000022.2:c.956_960del
NM_000022.3:c.956_960del
NM_001322050.1:c.551_555del
NM_001322051.1:c.884_888del
NR_136160.1:n.1042_1046del
NM_001322050.2:c.551_555del
NM_001322051.2:c.884_888del
NR_136160.2:n.983_987del

Pathogenic

Met criteria codes 2

PVS1 PP4_Strong

Not Met criteria codes 3

BS1 PM3 PM2

Evidence Links 0

Expert Panel

Severe Combined Immunodeficiency Disease VCEP

Criteria Specification Information

Criteria Specification: *ClinGen Severe Combined Immunodeficiency Disease Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for ADA Version 2.2*

Criteria Specification Approval History

Criteria Specifications for this VCEP

Evidence submitted by expert panel

Severe Combined Immunodeficiency Disease VCEP

NM_000022.4(ADA):c.956_960del (p.Glu319Glyfs*3) — also reported as c.955_959delAAGAG in older literature — is a 5-bp deletion in exon 10 causing a frameshift beginning at codon 319 with a premature termination codon predicted 3 residues downstream (~codon 322). This lies well upstream of the ADA-specific NMD-escape anchor at c.1028 (codon 343, exon 11), so the transcript is predicted to undergo nonsense-mediated decay. This prediction is directly supported by experimental data: Gossage et al. 1993 (PMID 8242080) reported a homozygous patient with "very low levels of ADA mRNA and protein," consistent with NMD, and Santisteban et al. 1993 (PMID 8227344) similarly found this deletion associated with severely reduced corresponding transcript levels in a heterozygous carrier (patient MJ). Therefore, PVS1 was met at full strength. The Grpmax filtering allele frequency of this variant is 0.00021203 (Non-Finnish European) in gnomAD v4, which is higher than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting, but lower than the BS1 threshold (>0.001611). Therefore, neither criterion is met. At least one proband (P3, Cagdas et al. 2018, PMID 29744787) meets diagnostic criteria for SCID with a T-B-NK- phenotype (0.5 pt); has profoundly reduced ADA enzyme activity, undetectable (0 nmol/h/mg), with elevated dAXP (71.9%) (5.0 pts); and presents with a T-B-NK- lymphocyte subset profile (0.5 pt). Total: 6.0 points, meeting PP4_Strong. In summary, this variant meets the criteria to be classified as Pathogenic for autosomal recessive severe combined immunodeficiency due to ADA deficiency based on the ACMG/AMP criteria applied, as specified by the ClinGen SCID VCEP: PVS1, PP4_Strong (VCEP specifications version 2.2).

Met criteria codes

PVS1	✔	This is a 5-bp deletion (c.956_960del, p.Glu319Glyfs*3; also reported as c.955_959delAAGAG in older literature) in exon 10, causing a frameshift beginning at codon 319 with a premature termination codon predicted 3 residues downstream (~codon 322). This lies well upstream of the ADA-specific NMD-escape anchor at c.1028 (codon 343, exon 11), so the transcript is predicted to undergo nonsense-mediated decay. This prediction is directly supported by experimental data: Gossage et al. 1993 (PMID 8242080) reported a homozygous patient with "very low levels of ADA mRNA and protein," consistent with NMD, and Santisteban et al. 1993 (PMID 8227344) similarly found this deletion associated with severely reduced corresponding transcript levels in a heterozygous carrier (patient MJ). Therefore, PVS1 was met at full strength.
PP4_Strong	✔	At least one proband (P3, Cagdas et al. 2018, PMID 29744787) meets diagnostic criteria for SCID with a T-B-NK- phenotype (0.5 pt); has profoundly reduced ADA enzyme activity, undetectable (0 nmol/h/mg), with elevated dAXP (71.9%) (5.0 pts); and presents with a T-B-NK- lymphocyte subset profile (0.5 pt). Total: 6.0 points, meeting PP4_Strong.

Not Met criteria codes

BS1	✖	The Grpmax filtering allele frequency of this variant is 0.00021203 (Non-Finnish European) in gnomAD v4, which is lower than the ClinGen SCID VCEP threshold (>0.001611) for BS1. Therefore, this criterion is not met.
PM3	✖	Cagdas et al. 2018 (PMID 29744787) report five unrelated probands homozygous for this variant, reflecting a founder effect in a Turkish cohort. Four probands (P3, P5, P10, P12) have documented consanguinity (0.5 pt each = 2.0 pts), and one proband (P13) is explicitly non-consanguineous (1.0 pt). Total: 3.0 points, meeting PM3_Strong. Because the Grpmax filtering allele frequency of this variant exceeds the PM2_Supporting threshold, PM3 was not applied following SCID-VCEP discussion on 9/25/2026,

PM2	✖	The Grpmax filtering allele frequency of this variant is 0.00021203 (Non-Finnish European) in gnomAD v4, which is higher than the ClinGen SCID VCEP threshold (<0.0001742) for PM2_Supporting for ADA. Therefore, this criterion is not met.

Curation History

Showing 1 to 1 of 1 rows

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.

ClinGen Terms of Use.
¤ Powered by BCM's Genboree.